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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PAPPU, SITA S	

ART UNIT	PAPER NUMBER
1632	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/802,445	Applicant(s) NEST ET AL.	
	Examiner Sita S Pappu	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-22 are pending in the instant application. This paper contains an examination of the claims 1-22 on their merits.

Priority

Applicant's claim to a benefit of provisional application 60/188,265 filed on 03/10/2000 is acknowledged.

Drawings

The drafts person objected to the drawings. See attached PTO-948. The drawings are acceptable for examination purposes only.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-8 are drawn to a method for preventing a symptom of papillomavirus infection in an individual who has been exposed to papillomavirus, comprising administering a composition comprising a polynucleotide comprising an immunostimulatory sequence to said individual.

The specification discloses the use of an immunostimulatory sequence (ISS) to treat and/or reduce the severity of symptoms and/or increase the recovery time of papillomavirus exposed dogs and rabbits. The specification does not disclose the use of the said ISS in preventing the symptoms of a human or animal papillomavirus infection. The disclosed use is limited to reducing the severity of, and not preventing, a symptom of papillomavirus infection in dogs and rabbits. Thus the specification is not enabling for claims 1-8 over any scope. This is particularly true when one considers the spontaneous regression experienced by dogs exposed to papillomavirus infection (see specification, page 43, last paragraph) and, thus, one cannot attribute the symptom prevention solely to the presence and/or activity of ISS and not to the spontaneous regression ability of the immune system. Specification on page 45 indicates that in CRPV-challenged rabbits "a number of viral DNA challenged sites failed to generate any papillomas". Specification fails to teach which treatment sites (ISS-treated or untreated) exhibited this result. The failure of papilloma generation in that particular experiment (on page 45 of the specification) seems to be the basis for the applicants' claim to prevent symptom formation (claims 1-8), and since the specification does not point out that the ISS-treated sites did indeed result in "no papilloma formation", it is unpredictable in which situation, papilloma formation was not seen. Thus, the specification is not enabling for claims 1-8 due to the insufficient guidance provided and further, due to the unpredictability of cancer gene therapy (as explained herein below), would have required a skilled artisan to engage in undue experimentation to practice the invention to prevent the symptom of papilloma infection.

Claims 9-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing severity of a symptom of papillomavirus infection in dogs and rabbits with papillomavirus, by administering a polynucleotide comprising an immunostimulatory sequence to said dogs and rabbits at a dose sufficient to reduce the severity of a symptom of papillomavirus infection, wherein the ISS comprises the sequence 5"-CG,pyrimidine, pyrimidine,CG-3', does not reasonably provide enablement for a method of reducing the severity of a symptom of papillomavirus infection in any individual or mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 9-22 are drawn to a method of reducing severity of a symptom of papilloma formation in an individual infected with papillomavirus, comprising administering a composition comprising a polynucleotide comprising an immunostimulatory sequence to said individual.

The specification is not enabling for a method of reducing the severity of a symptom of papillomavirus infection in any individual or mammal exposed to any human papillomavirus and any animal papillomavirus. The specification discloses the applicability of the claims to a method of reducing the severity of infection in dogs exposed to canine oral papillomavirus and rabbits exposed to cottontail rabbit papillomavirus.

In addition, claims 9, 10, 17, 18, claim the absence of a papillomavirus antigen. Dartmann et al (1986; Virology, vol.151, pp124-130) disclose the sequence, 5'-AACGTCCG-3' to be part of a human papillomavirus genome. The specification doesnot disclose the definition of the term "antigen", and therefore, the examiner is giving the term its broadest reasonable interpretation and considers any nucleic acid that can stimulate immune system as an antigen. Thus, due to the presence of the ISS sequence of the instant case within the papillomavirus genome and due to the said ISS being an immunostimulatory sequence and, therefore, being an antigen, the immunostimulatory effect shown by the ISS can be considered to be due to the said ISS being an antigen of papillomavirus origin. Thus the claims 9, 10, 17 and 18 are not enabled for the immunostimulatory effect shown by the ISS of the instant invention in the absence of papillomavirus antigen.

At the time of filing, *in vivo* gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of retroviruses, adenoviruses, or plasmid DNA/liposome complexes, was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery..", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Science, Vol. 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, " difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2,

and page 1055, column 1). Orkin et al. further states in a report to the NIH that, " [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin et al. (1995) "Report and recommendations of the panel to assess the NIH investment in research on gene therapy", page 1, paragraph 3, and page 8, paragraph 2).

Further, Mountain (2000; TIBTECH vol.18, pp119-128) states that the naked DNA delivery results in lower delivery efficiency than vectors, brief expression in most tissues and unsuitability for targeting and that it is a disadvantage for chronic-disease therapy (see page 124, left column, paragraph 2). Romano (2000; Stem Cells vol. 18, pp19-39) concurs and states that these limitations "make difficult the in vivo applications of nonviral gene delivery systems" (see page 30, right column, paragraph2, lines 3-6).

Krieg, A. M. (1999; J. Gene Med. Vol 1, pp 56-63) states that optimal ratio of CpG stimulatory motifs to CpG neutralizing motifs should be maintained in order to achieve an optimal immune response. Krieg further suggests that the immunostimulatory effect of the CpG nucleotides is achieved as a result of the unmethylated state of the immunostimulatory CpG motifs, and that it may have an unwanted effect of acute inflammatory response which could be exacerabated if the DNA uptake is enhanced by co-administration of lipids, as exemplified by studies in mice and cystic fibrosis patients, and further suggests that the generation of immune responses is to be avoided in any gene therapy application (page 59, right column, paragraph 3) considering the inflammatory reactions. Tokunaga (1999) concurs and

states that the ISS DNA may play an important pathogenic role in the inflammatory lung disease (page 8, left column, sub-section vi, paragraph 2).

Tokunaga et al (1999; Jpn. J. Infect. Dis. 52:1-11) further state that the activation of the immune system with ISS DNA could cause both beneficial as well as deleterious consequences (page8, left column, sub-section vi, paragraph 1) which is exemplified by the development of systemic lupus erythematosis (SLE) that was attributed to the ISS in bacterial DNA as a cause of over-expression of immune cytokines such as IL-6, and resistance to apoptosis, which there-by potentially allowed the survival of autoreactive cells (page 8, right column, paragraph 2). This suggests that studies in rabbits and dogs are not truly predictive of effects in other mammals and humans which is further supported as explained herein below.

Claims 5 and 13 are drawn to a mammal which includes humans. In many cases, studies in other animal systems do not reflect and/or predict success in human system. The specification enables the use of the method in only rabbits and dogs and does not predict success in humans. To put it in the words of Kmiec (1999; American Scientist, vol. 87, pp240-247), "limited success in animal models all too often leads directly to clinical trials" (page 245, middle column, paragraph 2, lines 1-3) and the quandary of human gene therapy is that "it sort of works" (page 246, right column, paragraph 3, lines 1-3). Thus, animal models are not truly reflective of success in humans and are thus, not predictive. Thus, it would require undue experimentation on the part of a skilled artisan to use the instant invention in any mammal or individual.

Thus, due to the art recognized unpredictability of achieving therapeutic levels of expression following direct administration of nucleic acids, the lack of guidance provided by the specification for the parameters affecting delivery and expression of therapeutic amounts of the ISS sequence, the lack of guidance concerning the prevention of the development of a symptom and reduction of the severity of symptoms in mammals and animals other than dogs and rabbits, and the breadth of the claims, it would have required undue experimentation to practice the instant invention and the skilled artisan would not have predicted success in reducing and/or preventing any and all papillomavirus infections in any and all mammals using the ISS of the instant case.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Dartmann et al. (1986).

The applicant claims an article of manufacture comprising a composition comprising an immunostimulatory sequence and instructions for administration of said composition. Instructions as to the use of a product are not given patentable weight in a product claim where the body of the claim does not depend on the preamble for completeness but, instead, the structural limitations are able to stand alone. The MPEP states that,".. in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art." In re Casey, 152 USPQ

235 (CCPA 1967); In re Otto , 136 USPQ 458, 459 (CCPA 1963) (MPEP 2111.02). Further, mere printed matter cannot impart a patentable feature to a claim (In re Gulack 217 USPQ 401 (1983).

Dartmann et al (1986; Virology, vol.151, pp124-130) disclose the sequence, 5'-AACGTCCG-3' to be part of a human papillomavirus genome, which encompasses the limitations of claim 17-22. Thus, by teaching all of the limitations of claims 17-22, Dartmann et al. clearly anticipates the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 9-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schlegel et al. (1999) and Sundaram et al. (1998), further in view of Dartmann et al. (1986), Krieg et al. (US patent No. 6218371) and Van Nest et al. (1999).

Schlegel et al. (1999 ; US patent no.5874089) teach that canine oral papilloma virus is responsive to vaccination with recombinant papilloma antigens (see column 34, paragraph 3). Similarly Sundaram et al. (1998; Vaccine, vol. 16. no. 6, pp613-623; see abstract, page 613) teach that cottontail rabbit papillomavirus (CRPV) is responsive to DNA vaccination with the L1 or E1 genes of the CRPV.

Schlegel et al (1999) and Sundaram et al. (1998) do not teach their findings with the ISS of the instant invention.

Dartmann et al. (1986; Virology, vol. 151, pp124-130) disclose the sequence AACGTCCG to be part of a human papillomavirus genome. Krieg et al.teach the sequence AACGTTCG in their patent (see column 45, complement of sequence 11) as an immunostimulatory sequence.

Dartmann et al. (1986) do not teach using their sequences as immunomodulators against COPV or CRPV infections.

Van Nest et al. (1999) and Sundaram et al (1998) provided the motivation to combine the teachings of Dartmann et al. and Krieg et al. and use the ISS of Dartmann et al. as an immunostimulatory sequence (as suggested by Krieg et al.) against rabbit and/or dog papillomavirus infection. Van Nest et al. (1999) demonstrated the ability of their ISS to stimulate immune responses to HBV vaccine in a variety of species

including mice, dogs, monkeys, baboons and other primates and suggested that the ISS has the potential for similar activity in human vaccine applications. Further, the teachings of Sundaram et al. (1998) suggest that DNA vaccination is a particularly attractive approach for papillomavirus-associated cancer, for exploring the efficacy of multiple vaccine strategies (page 621, right column, paragraph 3).

Further, since the sequence AACGTCCG of Dartmann et al, (1986) originates from papillomavirus, one of ordinary skill in the art would recognize that the sequence may function as a papillomavirus antigen that has an innate immunostimulatory capability being of homologous origin as the infecting virus.

Therefore, it would have been obvious to one of ordinary skill in the art to substitute the antigens of Schlegel et al. (1999) and Sundaram et al. (1998) with the ISS of Krieg et al. and/or Dartmann et al. (1986) and use it as claimed.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sita S Pappu whose telephone number is (703) 305-5039. The examiner can normally be reached on Mon-Fri (9:00 AM - 5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda can be reached on (703) 305-6608. The fax phone numbers

for the organization where this application is (703) 308-8724 for regular communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group patent analyst, whose telephone number is (703) 305-2758.

Anne-Marie Baker

ANNE-MARIE BAKER
PATENT EXAMINER

S. Pappu
December 13, 2001